PNEUMOCOCCAL DISEASE AFTER PNEUMOCOCCAL VACCINATION

An Alternative Method to Estimate the Efficacy of Pneumococcal Vaccine

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Abstract Trials of pneumococcal vaccine in healthy young adult populations suggest 75 to 95 per cent type-specific efficacy. Trials have not been done, however, in groups for which pneumococcal vaccine is currently recommended in the United States. To assess efficacy in the immunocompromised groups now receiving the vaccine, we compared serotypes of 35 isolates of *Streptococcus pneumoniae* isolated from blood or cerebrospinal fluid one month or longer after the patient had received commercially available pneumococcal vaccine with serotypes of 392 isolates from unvaccinated persons surveyed in a study of the nationwide distribution of pneumococcal serotypes. Proportions of infections with vaccine serotypes were unexpectedly similar. An alternative approach to estimation of vaccine efficacy suggested an average efficacy of 36 per cent in persons of all ages. The estimated efficacy was lowest in children two to 10 years old (≤0 per cent) and in persons with preexisting diseases that are thought to predispose to pneumococcal disease (≤0 per cent), and highest in the group over 10 years old (60 per cent). The possibility that efficacy is low in high-risk, immunocompromised populations makes it important to evaluate clinical efficacy and not just serum antibody responses in such groups. (N Engl J Med. 1980; 303:549-52.)

PNEUMOCOCCAL vaccine is currently recommended for use in persons over two years of age who have splenic dysfunction or certain chronic conditions associated with increased morbidity or mortality from pneumococcal disease, such as diabetes mellitus, nephrotic syndrome, multiple myeloma, cirrhosis, or alcoholism.[1] However, the trials that documented the clinical efficacy of the vaccine were performed in apparently healthy populations of young adults. Little evidence is available regarding clinical efficacy in the high-risk groups for which the vaccine is recommended — an unsatisfactory situation because these groups may well have impaired immunologic responsiveness. The low incidence of bacteremic pneumococcal disease and the problem of adequate documentation of the bacterial origin of pneumonia make it difficult to carry out prospective controlled trials in these groups. The greatest barrier to further controlled studies, however, may be the ethical problem of withholding a licensed product from the control group at high risk. In seeking an alternative approach for estimating the efficacy of pneumococcal vaccine in these groups, we used information collected after vaccine licensure and not based on randomized trials.

The vaccine consists of 14 pneumococcal capsular polysaccharide antigens, representing the most common disease-producing serotypes. Some of the 83 known types constitute antigenically related groups, indicated in the Danish system of nomenclature by a number for the group and a letter for the type within the group.[2] We hypothesized that since all the available evidence indicates that the vaccine is effective against the 14 polysaccharide types that it contains but not against other types, there should be a reduction in the incidence of vaccine-type pneumococcal infections in vaccinated persons, but no change in the incidence of nonvaccine-type infections. The proportion of isolates that are vaccine type should then be lower in the vaccinated population than in an unvaccinated population. We therefore compared the serotype distribution among pneumococci isolated from persons who had received the pneumococcal vaccine with the distribution in a nationwide surveillance study of pneumococcal serotypes in the general (largely unvaccinated) population.[3]

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METHODS

All clinical pneumococcal isolates from blood or cerebrospinal fluid submitted from May 1978 through January 1980 to the Center for Disease Control (CDC) for serotyping were included in this study if accompanying information indicated that the patient had received pneumococcal vaccine and was over two years of age at the time of the vaccination. The patients' records were reviewed to determine age, sex, date of vaccination, date of onset, clinical syndrome, underlying disease, and outcome of episode if these data were not specified on the laboratory form. We also confirmed that the serotype of the isolate was unknown before submission to the CDC. Serotype distribution in an unvaccinated population was determined on the basis of blood and cerebrospinal-fluid isolates from patients over two years of age. These isolates were a subset of those submitted to the CDC in a nonrandom sample of 46 hospitals in 26 states as part of a nationwide study.[3] Participating hospitals were asked to submit all pneumococci isolated from blood and cerebrospinal fluid. Information was requested to confirm that the patients were unvaccinated and to determine age, sex, clinical syndrome, underlying disease, and outcome of episode.

Pneumococci were identified on the basis of ethylhydrocupreine (Optochin) susceptibility, bile solubility, and capsular swelling with specific antiserums. Serotyping was performed at the Streptococcus Reference Laboratory, Bureau of Laboratories, with type-specific antiserums made by the Biological Products Division, Bureau of Laboratories, CDC.

Vaccine efficacy is defined as the percentage reduction in the risk of vaccine-type infections in vaccinated as compared with unvaccinated persons. On the basis of the categories shown in Table 1,

$$\text{estimated efficacy } (\hat{E}) = \frac{c/N_2 - a/N_1}{c/N_2} = 1 - \frac{N_2 a}{N_1 c} \qquad (1)$$

However, since we assume that there is no change in the risk of nonvaccine-type infections in the vaccinated population, it can be estimated that

$$\frac{b}{N_1} = \frac{d}{N_2}; \frac{N_2}{N_1} = \frac{d}{b} \qquad (2)$$

Table 1. Categories of Vaccinated and Unvaccinated Persons.

Status	Category			Total No. of Persons
	Diseased		Healthy	
	vaccine type	*nonvaccine type*		
Vaccinated	a	b	$N_1-(a+b)$	N_1
Not vaccinated	c	d	$N_2-(c+d)$	N_2

When Equation 2 is substituted in Equation 1,

$$\hat{E} = 1 - \frac{ad}{bc}. \quad (3)$$

Equation 3 indicates that the only datum needed to estimate efficacy is the number, not the rate, of pneumococcal infections in each category in Table 1.

The validity of the assumption that underlies Equation 2 can be verified by examination of data from early randomized trials of pneumococcal vaccine (Table 2). Although the attack rates vary markedly from trial to trial according to the methods employed, the rates of nonvaccine-type disease are remarkably similar in the placebo and vaccinated groups within each trial.

In these randomized placebo-controlled trials, there is an equal risk of pneumococcal disease in both the vaccinated and placebo groups. However, the same formula can be derived if a constant ratio of risk of pneumococcal disease is assumed in the two populations. If k equals the relative risk of pneumococcal disease in the vaccinated population if it were not vaccinated, as compared with the risk of pneumococcal disease in the unvaccinated population being studied, the efficacy can be calculated by the formula

$$\hat{E} = \frac{kc/N_2 - a/N_1}{kc/N_2} = 1 - \frac{N_2 a}{N_1 kc} \quad (4)$$

$$\frac{b}{N_1} = \frac{kd}{N_2}; \frac{N_2}{N_1} = \frac{kd}{b} \quad (5)$$

$$\hat{E} = 1 - \frac{ad}{bc}$$

The estimate does depend on a similar proportion of vaccine-type and nonvaccine-type disease in unvaccinated populations. Data to support this assumption are available from investigations in this country and Europe of isolates from patients with invasive disease. Despite changes in presence of individual serotypes, the proportion of isolates of groups represented in the current vaccine formulation was 77 to 81 per cent.[7-10] These figures are based on results in vaccine groups because it was not possible in the studies to distinguish all 83 types. However, type-specific data from the CDC surveillance project also show no notable difference in proportion of vaccine-type isolates according to geographic location, type of hospital, type of specimen, age of patient, or presence of underlying medical conditions predisposing to pneumococcal disease.[3]

Table 2. Similarity of Attack Rates of Nonvaccine-Type Pneumococcal Disease in Vaccinated and Unvaccinated Populations.

Status	Cases of Nonvaccine-Type Disease	Total Population	Attack Rate	Reference
Vaccinated	11	3453	0.0032	Ekwurzel et al[4]
Unvaccinated	16	4942	0.0032	
Vaccinated	56	2044	0.027	MacLeod et al[5]
Unvaccinated	59	2118	0.028	
Vaccinated	14	1490	0.009	Austrian[6]
Unvaccinated	43	3007	0.014	

A final assumption is that cultures would be obtained with equal frequency before treatment of infections caused by different pneumococcal types.

Ninety-five per cent confidence limits of vaccine efficacy were derived with the method of Miettinen.[11]

Results

Thirty-five pneumococcal isolates from vaccinated persons were received between May 1978 and January 1980 (Table 3). Twenty-two of the isolates were types included in the current vaccine formulation, three were serologically related to vaccine types (6B, 18B, and 19A), and 10 were not vaccine types. The most common vaccine serotypes isolated from vaccinated persons were 6A, 19F, and 23F (four isolates each). Eleven of the isolates were from patients under 10 years of age. Ten of the 11 isolates from children were vaccine types, and one was a vaccine-related type, whereas only 12 of the 24 isolates from adults were vaccine types ($P = 0.02$, Fisher's exact test). Twenty-four of the patients were male, and 11 female. Nineteen of the male patients but only four of the female patients had vaccine-type isolates ($P = 0.01$, Fisher's exact test). All had been vaccinated one to 18 months before the onset of illness; the intervals between vaccination and onset were similar for those with vaccine-type and nonvaccine-type infections. Preexisting disease was present in all patients; of 19 who had undergone splenectomy, three had Hodgkin's disease. Three of the 10 cases with a nonvaccine-type isolate died, as compared with only two of the 22 cases with a vaccine-type isolate.

The serotype distribution among the isolates from vaccinated persons and the corresponding data from the national study are shown in Table 4. Since it is not known whether the vaccine protects against disease caused by any or all of the serologically related types, the first estimate of efficacy ($\hat{E}_1$ in Table 4) uses the number of vaccine-type and nonvaccine-type episodes but excludes episodes caused by serologically related types. The estimated vaccine efficacy is $\hat{E}_2$ if equal protection is conferred against vaccine types and serologically related types, and $\hat{E}_3$ if no protection occurs against the related types. The overall estimate of vaccine efficacy by the first method is 36 per cent (95 per cent confidence limits, ≤ 0 to 77 per cent). However, when the data are stratified according to age and preexisting disease, the efficacy appears to be minimal in the pediatric group and the group with preexisting disease and highest in the group over 10 years of age, although the small number of isolates in each subgroup precludes definite conclusions. Estimates of vaccine efficacy do not differ much if the serologically related types are excluded or if they are combined with the vaccine types ($\hat{E}_1$ vs. $\hat{E}_2$).

Discussion

There have been recent reports of disease caused by vaccine-type pneumococci in vaccinated persons who have an underlying disease such as sickle-cell disease

Table 3. Pneumococci Isolated after Pneumococcal Vaccination in 35 Patients.

Type	Source *	Time after Vaccination (mo)	Age at Vaccination (yr)	Sex	Treatment, Condition, or Preexisting Disease †	Clinical Syndrome
1 ‡	Blood	8	78	M	COPD; transient ischemic attacks	Pneumonia
1 ‡	Blood, CSF	12	28	M	Splenectomy; post-trauma	Meningitis
3 ‡	Blood	14	59	F	COPD	Pneumonia
3 ‡	Blood, CSF	4	3	M	Splenectomy; post-trauma	Sepsis §
4 ‡	Blood, PF	1	4	M	Nephrotic syndrome	Peritonitis
6A ‡	Blood	4	75	M	Parkinson's disease	Pneumonia
6A ‡	Blood	12	2	M	Splenectomy; hemolytic anemia	Pneumonia
6A ‡	Blood	18	13	M	HD	Sepsis
6A ‡	Blood, CSF	6	39	M	Splenectomy; lymphoma	Meningitis
6B	CSF, blood	2	78	F	Elderly	Meningitis
8 ‡	Blood	7	57	M	Chronic lymphocytic leukemia; low immunoglobulins	Pneumonia
11A	Blood	17	57	F	Diabetes mellitus	Pneumonia
14 ‡	Blood	4	8	F	Splenectomy; HD	Sepsis
14 ‡	CSF	12	16	M	Splenectomy; HD	Meningitis
14 ‡	Blood, PF	3	2	M	Nephrotic syndrome; intermittent steroids	Peritonitis
15B	CSF	1	72	F	Splenectomy	Meningitis §
15B	Blood	18	13	F	Splenectomy; hemolytic anemia	Meningitis
16	Blood	10	78	M	COPD; aortic-valve prosthesis	Pneumonia
18B	Blood	2	17	M	Splenectomy; post-trauma	Sepsis
18C ‡	CSF	6	9	M	Splenectomy; congenital hemolytic anemia	Meningitis §
19A	Blood	12	3	M	Sickle-cell disease	Pneumonia
19F ‡	CSF	8	2	M	Splenectomy; chronic myeloproliferative disorder	Meningitis
19F ‡	Blood	11	65	F	Bronchiectasis, COPD	Pneumonia
19F ‡	Blood	7	4	M	Splenectomy; ITP	Sepsis
19F ‡	Blood	7	3	M	Sickle-cell disease	Pneumonia
22F	Blood, CSF	7	62	F	Splenectomy; ITP	Meningitis §
22F	Blood	3	30	M	Splenectomy; post-trauma	Pneumonia
22F	Blood	4	61	F	Low immunoglobulins	Pneumonia
22F	Blood	5	63	F	Splenectomy; ITP	Pneumonia
22F	Blood	7	29	M	Splenectomy; HD	Meningitis
22F	Blood	12	11	M	Splenectomy; post-trauma	Sepsis §
23F ‡	CSF	13	58	M	COPD	Meningitis
23F ‡	CSF, blood	2	16	M	Splenectomy; hemolytic anemia	Meningitis
23F ‡	CSF	3	47	M	Splenectomy	Meningitis
23F ‡	Blood	10	2	F	Sickle-cell disease	Pneumonia

*CSF denotes cerebrospinal fluid, and PF peritoneal fluid.

†COPD denotes chronic obstructive pulmonary disease, HD Hodgkin's disease, and ITP idiopathic thrombocytopenic purpura.

‡Vaccine-type isolate.

§Fatal outcome.

or who have undergone splenectomy.[12-14] Such anecdotal episodes of vaccine failure would be expected even if the vaccine were as effective in persons to whom it is now being given as it was in those in the clinical trials — an estimated 75 to 95 per cent[9,15] — but such episodes indicate the need to measure the efficacy of the vaccine in groups now receiving it. Our data, although based on a small number of isolates, suggest that the efficacy of the vaccine may be considerably less in children and in patients with underlying disease than in the generally healthy adults studied in prelicensure clinical trials.

This finding is consistent with the finding of defects in antibody production to the capsular polysaccharides noted in certain groups of patients with underlying disease. Several investigators have noticed defects in antibody production in patients undergoing therapy for Hodgkin's disease.[16,17] Although patients with the nephrotic syndrome have been noted to have proportionate rises in antibody titer that are similar to

Table 4. Estimated Efficacy of Pneumococcal Vaccine in Selected Groups.

Group	Number of Persons			E_1†	E_2‡	E_3§
	With vaccine type*	With serologically related type	With nonvaccine type	per cent		
Total group						
Vaccinated	22 (63)	3	10	36	39	17
Unvaccinated	263 (67)	52	77			
Group 2–10 years old						
Vaccinated	10 (91)	1	0	— ¶	—	<0
Unvaccinated	45 (73)	12	5			
Group >10 years old						
Vaccinated	12 (50)	2	10	60	61	49
Unvaccinated	218 (66)	40	72			
Patients at high risk of pneumococcal morbidity or mortality ‖						
Vaccinated	15 (63)	2	7	<0	<0	<0
Unvaccinated	19 (56)	4	11			

*Figure in parentheses is percentage of total number of isolates.

†E_1 = efficacy estimated by comparison of vaccine-type vs. nonvaccine-type isolates.

‡E_2 = efficacy estimated by comparison of vaccine-type plus serologically related types vs. nonvaccine-type isolates.

§E_3 = efficacy estimated by comparison of vaccine-type vs. serologically related type plus nonvaccine-type isolates.

¶Cannot be calculated.

‖Patients with asplenia, sickle-cell anemia, Hodgkin's disease, renal failure, multiple myeloma, or cirrhosis.

those in control groups, the geometric mean of antibody concentrations after vaccination against Types 1, 14, and 23F were, at most, one-quarter as high as in control patients.[18] Similarly, asplenic patients, excluding those with Hodgkin's disease, had generally comparable postvaccination titers, except that titers to Types 9, 12, and 14 were less than half those of normal control patients.[19] Whether failure of the vaccine to protect some people can be ascribed directly to inadequate antibody response or is related to another defect in the immune system is not known. However, the apparent lack of clinical efficacy observed in our study among some groups suggests that it is important either to determine the characteristic of antibody response that correlates directly with clinical efficacy or to determine clinical efficacy directly in these groups.

Logistical considerations may make it impossible to evaluate the efficacy of new vaccines for all categories of patients at high risk before licensure. However, licensure of a vaccine should not preclude further controlled trials in groups that may have immune responses different from those in the populations studied in prelicensure trials. Postlicensure surveillance will be important in identification of groups that may need further study. This alternative method for estimation of vaccine efficacy may be the most reasonable way to use surveillance data to estimate efficacy for specific categories of patients and verify the need for further prospective controlled trials.

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